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<p>(21) International Application Number: PCT/GB96/02746 (22) International Filing Date: 8 November 1996 (08.11.96) (30) Priority Data: 9523066.0 10 November 1995 (10.11.95) GB (71) Applicant (for all designated States except US): CHIRO-SCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): POPE, Nicholas, Robert [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). WILLIS, Ruth, Elizabeth [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (74) Agent: GILL JENNINGS &amp; EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: MATRIX METALLOPROTEINASE INHIBITORS AND THEIR THERAPEUTIC USE (57) Abstract A matrix metalloproteinase inhibitor is used for the treatment of a subject of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, wherein the treatment is conducted after surgical operation on the subject, and wherein the inhibitor exhibits an IC<sub>50</sub> of below 100 μM with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.</p>		

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MATRIX METALLOPROTEINASE INHIBITORS AND THEIR  
THERAPEUTIC USE

Field of the Invention

This invention relates to the therapeutic use of  
5 compounds that inhibit matrix metalloproteinases.

Background of the Invention

Compounds having the ability to inhibit matrix  
metalloproteinases (MMP) and optionally also the release of  
tumour necrosis factor, e.g. TNF $\alpha$ , are described in US  
10 Patent Applications Serial Nos. 08/539,578, filed May 10,  
1995, and 08/644,381, 08/644,383, 08/644,797 and  
08/644,802, all filed May 10, 1996, and in WO-A-9513289,  
PCT/GB96/01135, PCT/GB96/01136, PCT/GB96/01137,  
PCT/GB96/01138, PCT/GB96/02438 (and corresponding US  
15 Application filed Oct. 5, 1996) and PCT/GB96/02439.  
Various effects of these inhibitory activities are  
described, as are suitable formulations and dosages. The  
specifications of all these Applications are incorporated  
herein by reference.

20 Other compounds of this general type are also known.  
Activity can be determined by any or all of the tests  
described in Examples A-G of WO-A-9611209 (described herein  
as "Example A" etc).

Summary of the Invention

25 This invention is based on the appreciation that  
compounds having particularly valuable properties are of  
the type which reduces circulating levels of TNF $\alpha$  with or  
without activity against the classical MMP's, and that  
circulating levels of interleukin-1 $\beta$  (and also IL-6) may  
30 also be reduced. This effect may be defined in terms of a  
specific range of activity in defined models for both TNF  
and IL-1 $\beta$  effects. The benefits arising from this  
invention are due to two factors. Firstly, there is  
synergy between TNF $\alpha$  and IL-1 $\beta$  in the body, so that a  
35 partial reduction in both of these may well have a larger  
effect clinically than a total reduction in just one of  
them (that is TNF $\alpha$ ). Secondly, a complete reduction in

TNF $\alpha$  levels may be detrimental. According to this invention, the combined partial inhibition of these two cytokines should overcome this detrimental influence and yet provide as good if not better efficacy.

5 In particular, compounds to which this invention relates have two or more of characteristics x, y and z, wherein:

x = MMP Inhibition, in terms of IC<sub>50</sub> according to Example a, b or c (see above).

10 y = TNF $\alpha$  Inhibition, in terms of IC<sub>50</sub> according to Example D of Application No. PCT/GB96/01136.

z = IL-1 Inhibition, in terms of Example D of Application No. PCT/GB96/01136, modified by using a commercially-available IL-1 $\beta$  kit (R & D Systems) to assay  
15 the supernatant for IL-1 $\beta$ , determining the activity in the presence of 1 mM inhibitor or dilutions thereof by comparison to activity in a control devoid of inhibitor, and reporting IC<sub>50</sub> as that inhibitor concentration effecting 50% inhibition of the production of IL-1 $\beta$ .

20 x is below 10<sup>-4</sup> M, preferably below 10<sup>-6</sup> M, more preferably 10<sup>-6</sup> M to 10<sup>-9</sup> M.

y is below 10<sup>-4</sup> M, preferably 10<sup>-4</sup> M to 10<sup>-7</sup> M, more preferably 5 x 10<sup>-5</sup> M to 10<sup>-6</sup> M.

z is below 10<sup>-4</sup> M, preferably 10<sup>-4</sup> M to 10<sup>-7</sup> M, more  
25 preferably 5 x 10<sup>-5</sup> M to 10<sup>-6</sup> M.

The range for z is especially interesting, since it is distinct from most prior art compounds having characteristic x. Nevertheless, this invention relates to compounds having all three characteristics, or any two  
30 characteristics with relative inactivity according to the other, eg. IC<sub>50</sub> above 5 x 10<sup>-4</sup> M.

Compounds as defined above may be used in a method of treatment (which term includes prevention and prophylaxis) of the animal, and especially human, body, in post-operative care (whether in or out of hospital). The  
35 treatment regime may be a continuation of that given before the operation, e.g. for arthritis, asthma, cancer or any

other condition susceptible to treatment with a MMP inhibitor. They may also be used where the subject is susceptible to the recurrence of lymphoma.

Description of the Invention

5 Compounds that meet the criteria given above are described in the specifications identified above. Specific examples of such compounds are given in the Table, below. The first and second listed compounds, and the third on the second page are in WO-A-9513289; the last two are in  
10 PCT/GB96/01136; and the others are in WO-A-9611209; reference should be made to the formulae therein. Suitable compositions, dosages etc. of such compounds are also described in the specifications identified above. The same considerations may be applied in use of the present  
15 invention.

Evidence is emerging from clinical studies conducted using specific molecular antibodies against TNF $\alpha$  that a complete reduction of TNF $\alpha$  levels in the blood of patients with rheumatoid arthritis gives rise to relatively high  
20 frequency of decidedly negative side-effects. These are of two forms, one being a reduction of the body's resistance to infection from outside agents. The frequency of serious infections in these patients is significantly increased. Secondly, an increase in the incidence of cancer in these  
25 patients, i.e. lymphoma, may occur. These symptoms may be due to the same effect, namely a reduction in the body's resistance to "foreign" agents.

Compounds of the type generally described herein may thus be particularly useful for the therapeutic indications  
30 described in the specifications of the Applications identified above. Thus, for example, the compounds of WO-A-9513289 may be useful for the expanded range of indications described in WO-A-9611209.

Reduction of the potential side-effects of cancer or  
35 infection may be particularly beneficial following surgery. In particular, post-operative infection in patients undergoing operation for cancer removal or, for example,

hip or other joint replacement, may be treated. Treatment is enhanced in situations where the potential enhancement in susceptibility to infection due to TNF reduction is coincident with the treatment of the disease. In other words, a suitable MMP inhibitor may be used to treat cancer patients concomitant with surgery, where that treatment may give rise to an increased tendency to post-operative infection, such as a nosocomial infection. Similarly, such a compound may be used during and after hip replacement and for the treatment of rheumatoid arthritis or osteoarthritis. The partial inhibition of TNF and optionally also of IL-1 rather than total TNF inhibition coincident with MMP inhibition is intended to give a benefit in reducing potential side-effects that the surgery had made the patient prone to. Further, the compounds defined herein are of benefit in reducing the occurrence of lymphoma.

					IC <sub>50</sub> (μM)	
R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	TNF	IL-1
Ac	H	H	i-Bu	CH <sub>2</sub> Ph	10.2	17.5
H	H	H	i-Bu	CH <sub>2</sub> Ph	22.7	22.6
Ac	H	H	CH <sub>2</sub> SMc	CH <sub>2</sub> Ph	31	38
H	H	H	CH <sub>2</sub> SMc	CH <sub>2</sub> Ph	9	62
Ac	(CH <sub>2</sub> ) <sub>2</sub> NPhMn	H	i-Pr	CH <sub>2</sub> Ph	14	51
Ac	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Me	H	n-heptyl	CH <sub>2</sub> Ph	11	12.9
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	CH <sub>2</sub> SMc	CH <sub>2</sub> Ph	5.5	11.2
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	n-Pr	CH <sub>2</sub> Ph	9.3	8.6
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	CH <sub>2</sub> SMc	CH <sub>2</sub> -3-indolyl	15.8	1A
H	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	CH <sub>2</sub> SMc	CH <sub>2</sub> -3-indolyl	7.1	47
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> -3-indolyl	16.8	1A
H	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> -3-indolyl	35	1A
Ac	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Me	H	i-Bu	CH <sub>2</sub> -3-indolyl	38	22
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Pr	(CH <sub>2</sub> ) <sub>3</sub> NHBoc	15	37
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	t-Bu	11.6	22
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	C(Me) <sub>2</sub> SMc	6.4	24
Ac	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> Ph	5.8	11.2
H	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> Ph	6.2	18.7
Ac	(S)-(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> Ph	6.6	21.8
H	(S)-(CH <sub>2</sub> ) <sub>3</sub> NPhMn	H	i-Bu	CH <sub>2</sub> Ph	24	1A
Ac	(CH <sub>2</sub> ) <sub>2</sub> Ph	H	i-Bu	CH <sub>2</sub> Ph	24	1A
Ac	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Me	H	i-Bu	CH <sub>2</sub> Ph	29	11
Ac	(CH <sub>2</sub> ) <sub>3</sub> SAC	H	i-Bu	CH <sub>2</sub> Ph	5	25
H	H	(CH <sub>2</sub> ) <sub>3</sub> NPhMn	i-Bu	CH <sub>2</sub> Ph	8	6
H	H	(CH <sub>2</sub> ) <sub>2</sub> NPhMn	i-Bu	CH <sub>2</sub> Ph	25	4

CLAIMS

1. Use of a matrix metalloproteinase inhibitor for the manufacture of a medicament for the treatment of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, wherein the treatment is conducted after surgical operation on the subject, and wherein the inhibitor exhibits an  $IC_{50}$  of below  $100\ \mu M$  with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.
2. Use of a matrix metalloproteinase inhibitor for the manufacture of a medicament for the treatment of a subject susceptible to or exhibiting a condition that can be treated with the inhibitor, and susceptible to recurrence of lymphoma, and wherein the inhibitor exhibits an  $IC_{50}$  of below  $100\ \mu M$  with respect to matrix metalloproteinase and causes no or a partial reduction in levels of tumour necrosis factor.
3. Use according to claim 1 or claim 2, wherein the  $IC_{50}$  (MMP) is below  $1\ \mu M$ .
4. Use according to claim 3, wherein the  $IC_{50}$  (MMP) is between  $1\ nM$  and  $1\ \mu M$ .
5. Use according to any preceding claim, wherein the  $IC_{50}$  (IL-1) is between  $0.1$  and  $100\ \mu M$ .
6. Use according to claim 5, wherein the  $IC_{50}$  (TNF $\alpha$ ) is between  $1$  and  $50\ \mu M$ .
7. Use according to any preceding claim, wherein the  $IC_{50}$  (TNF $\alpha$ ) is below  $100\ \mu M$ .
8. Use according to claim 7, wherein the  $IC_{50}$  (TNF $\alpha$ ) is between  $0.1$  and  $100\ \mu M$ .
9. Use according to claim 7, wherein the  $IC_{50}$  (TNF $\alpha$ ) is between  $1$  and  $50\ \mu M$ .



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/02746

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 13289 A (CHIROSCIENCE LIMITED) 18 May 1995 cited in the application see the whole document ---	1-9
P,X	WO 96 11209 A (CHIROSCIENCE LIMITED) 18 April 1996 cited in the application see the whole document ---	1-9
E	WO 96 35711 A (CHIROSCIENCE LIMITED) 14 November 1996 cited in the application see the whole document -----	1-9

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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